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Attachment of Ketide Side Chains on Methyl-1,4-naphthoquinones for Biomimetic Type Angucycline Syntheses

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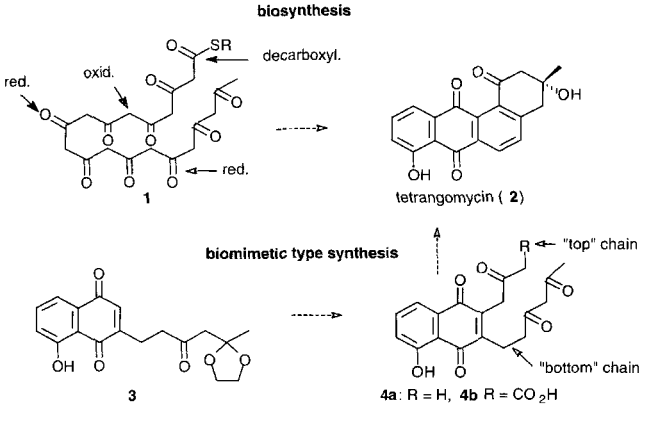
Abstract. The Michael addition of nucleophiles **5–10** derived from β-ketoesters with the methyl-1,4-naphthoquinones **16** and **20** was systematically investigated in connection with a biomimetic type synthesis of angucyclinone antibiotics. Drawbacks of these reactions were the formation of regioisomers (e.g. **12/13** and **18/19**), unwanted cyclizations (**14** and **15**), and occasional 1,2-addition (**23**). No side reactions and a good overall yield (80%) in the attachment of a C_3-2-oxo-side chain was achieved by Stille reaction of allyl stannane **11** with the bromoquinone **24** followed by cleavage of the double bond to yield ketone **26**.

In connection with biomimetic type syntheses of quinone antibiotics [1, 2] we investigated the possibility of attaching various oligoketide side chains to a naphthoquinoide core. A short generalized idea of the biosynthesis of angucyclines *via* the hypothetic decaketide **1** leading to the angucyclinone tetrangomycin (**2**) is depicted in Scheme 1. For biomimetic type syntheses efficient procedures have to be found for the sequential attachment of oligoketide fragments to ring systems *via* **3** and **4a/b** to restrict the manifold uncontrolled aldol condensation of long chain polyketides [3].



Scheme 1

Practical solutions for tri- or diketo "bottom" C_6-side chaines were previously found by our group using a Baker–Venkataraman rearrangement of (*ortho*-acetyl) acyloxy compounds [1] or the alkylation of β-ketoesters with halomethylquinones followed by dealkoxycarbonylation [4]. The attachment of the "top" C_4-1,3-dicarbonyl fragments was possible by the reaction of nucleophiles with acetyl-1,4-naphthoquinones which are extremely potent Michael acceptors [1]. However, cyclization of the 2-acyl-quinones leads to *linearly* condensed molecules (i.e. alkanonic acid and anthracyclines). The electron deficient bromojuglones are also good Michael acceptors [5] but they cannot be used in this context. To direct the cyclization into an *angular* mode (e.g. angucyclines, name: [6], review: [7]) the carbonyl group at C-1' (e.g. the one directly attached to the quinone core) has to be omitted as shown in the biomimetic type synthesis of Scheme 1 illustrating the stepwise transformation of **3** via **4a** or **4b** to tetrangomycin (**2**) [2]. Thus, the attachment of ketide fragments on *alkylated* (and not acylated) 1,4-naphthoquinones was required for biomimetic type angucycline synthesis (Scheme 1).

In this investigation seven different nucleophilic building blocks **5–11** (Chart 1) which are either commercially available (**5**, **6**, **8**) or easily to be prepared (**7** [8], **9** [5], **10** [5] **11** [9]) (Chart 1) were studied in the

reaction with methyl-1,4-naphthoquinones **16** and **20**. It should be mentioned that the reactions were carried out in the presence of dichlorodicyano benzoquinone (DDQ) for a rapid reoxidation of the hydroquinones formed after the Michael addition by tautomerization of the initially formed 1,4-diones. In the absence of oxidation agents the hydroquinones would reduce the quinone starting material (the redox equilibrium is rapidly established in alkaline medium) and thus stop the reaction at a relatively early stage.

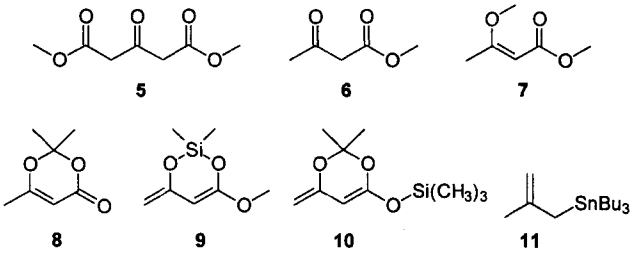
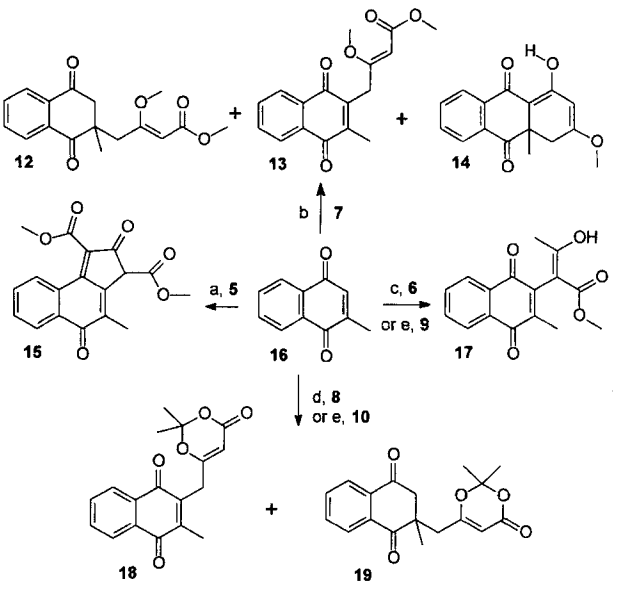


Chart 1

We started the testing with acetonedicarboxylic ester **5** in the reaction with the methylated 1,4-naphthoquinones **16** and **20** (Schemes 2 and 3). It was possible that the intermediate 1,4-diones resulting from the Michael addition would tautomerize to the 1,4-naphthalenediols to form lactones by intramolecular transesterification with the nucleophilic phenolic hydroxy group. A differentiation between the two ester groups in the Michael adduct and subsequent selective decarboxylation could thus be possible. However, no lactone but rather the benzoindene system **15** was formed in the reaction of **5** with **16**. Apparently, an open chain adduct similar to **21** which could be isolated in the reaction of **5** with methyljuglone **20** (see Scheme 3) underwent an intramolecular aldol type condensation.

Since the required differentiation of the two ester groups of **5** was not possible, we turned our attention to acetoacetic ester **6** as the nucleophile. In this case, the *dianion* of **6** had to be reacted with the quinone **16** to obtain the desired linear C_4-chain attachment. But again, the expected product could not be isolated and in addition to many polar decomposition polymers only the C_2-adduct **17** was identified, resulting from addition of the stabilized monoanion of **6** (Scheme 2).

To avoid the unfavorable strong basic conditions necessarily connected with the generation of the dianions of **6**, the enol ether **7** prepared from **6** [8] was studied next. The required C–H acidity in **7** is located by vinylology at the terminal carbon atom generating a relatively soft stabilized monoanion ideally suited for Michael addition [compare 10]. In fact, an even more



[a]) NaH, THF, 22 °C, 24 h, **15** (5.5%); [b]) 1 equiv. of LDA, DDQ, THF, 0 °C, 8 h, **12** (39%), **13** (24%), **14** (8%); [c]) 2.2 equiv. of LDA, DDQ, THF, – 78 °C **17** (6.6%); [d]) 1 equiv. of LDA, DDQ, THF, 0 °C, 2 h, **18** (31%), **19** (43%); [e]) i. CsF, 18-crown-6, THF, – 60 °C, 6 h, ii. Ag_2O, 1 h, **17** (11%)

Scheme 2

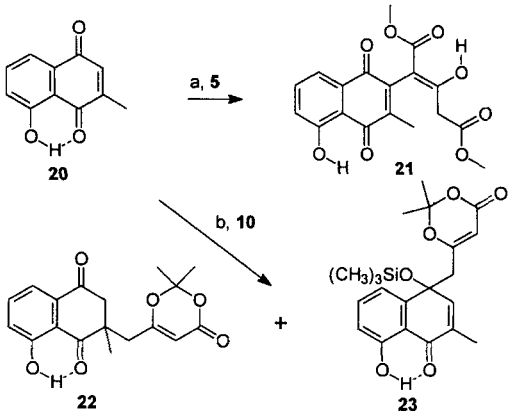
selective reaction of **7** with menadione (**16**) was observed and the adducts **12** (39%) and **13** (24%) were the major products. A more regioselective reaction towards addition to the less hindered site at C-3 might be expected by the reaction of quinones with longer side chains at C-2. In addition to **12** and **13**, the cycloaddition product **14** was isolated in low yield (8%). The product is possibly formed by ester condensation with the activated methylene group at C-3. However, a concerted cycloaddition cannot be ruled out in the formation of **14**.

To limit the conformational flexibility which favored the formation of the tricylus **14**, the 1,3-dioxine **8** with a fixed transoid dienolate structure of the corresponding anion, was tested next in the reaction with quinone **16**. In fact, our assumption was confirmed and only the open chain adducts **18** (31%) and **19** (43%) were isolated in an acceptable combined yield without giving rise to the formation of unwanted cyclization products such as **14**.

Encouraged by the promising results with the dioxane **8**, we next turned our attention to the silylated derivatives **9** and **10** [5]. In the reaction with these silylenol ethers, basic conditions which are sometimes disadvantageous in the conversion of quinones, could be avoided. However, only the adduct **17**, already observed in the addition of acetoacetate **6** to **16**, could be isolated in the caesium fluoride mediated reaction of **16** with **9**. A selective reaction at C-4 of the nucleophile was observed with the acetonide **10** which gave the same prod-

ucts **18** and **19** already isolated with the dioxolane **8** under basic conditions, albeit in much lower yields.

Interestingly, in the reaction of **10** with 2-methyl-juglone (**20**), in addition to **22**, the product **23** was formed by 1,2-addition to the naphthoquinone carbonyl group in low yield (2%) (Scheme 3).



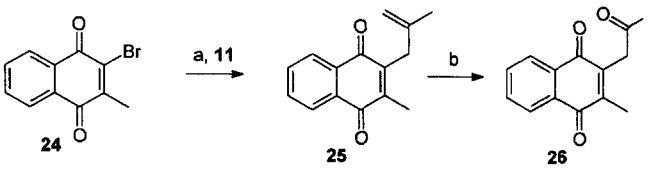
a) i. THF, 22 °C, 24 h, ii. Ag_2O, 1 h, **21** (5%);
b) $SnCl_4$, THF, −78 °C, **22** (8%), **23** (2%)

Scheme 3

The disappointing results with the silyl ethers **9** and **10** and also the missing high selectivity in the reaction with the acetonide **8** necessitated an entirely different strategy. In the course of our synthetic scheme, brominated naphthoquinones were intermediates. Thus, instead of reductively removing the bromine to unreveal the electrophilicity for the subsequent Michael reaction with nucleophiles **5**–**10**, we anticipated the use of the bromine atom in a Stille type palladium catalyzed coupling with allylstannanes [11]. This strategy also solved the problem of regiochemistry since the bromine determines the addition site of the alkyl chain. The use of the Stille reaction was further encouraged by an investigations of Echavarren et al. who extended the Stille reaction to halogenated 1,4-naphthoquinones also stating the favorable effect of the addition of copper salts as cocatalysts [12, 13].

The easily available 2-bromo-3-methyl-1,4-naphthoquinone **24** [14] was selected as the model in the reaction with the methallyl stannane **11** [9]. The positive effect of the copper cocatalyst (CuBr) could be confirmed and the adduct **25** was isolated in 93% yield (Scheme 4).

The synthetic scheme envisioned the cleavage of the double bond of the side chain to generate the carbonyl group. Ozonolysis was successfully used in the anthraquinone series [15] but could not be applied with the naphthoquinone **25** due to the oxidative destruction of the naphthoquinone core as indicated by rapid de-



a) $Pd(P\{C_6H_5\}_3)_4$, CuBr, dioxane, reflux, 7h, **25** (93%);
b) OsO_4, $NaIO_4$, dioxane, H_2O, 22 °C, 24 h, **26** (86%).

Scheme 4

colorization in the initial phase of the ozonolysis (compare [16]). However, the Lemieux–Johnson procedure [17] (osmylation in presence of excess periodate) gave the desired ketone **26** in 86% yield without substantial destruction of the naphthoquinone core. The methodology is presently extended to dienyl stannanes to afford the 1,3-dicarbonyl side chain.

In summary, the anion generated from the 1,3-dioxolane **8** is a good nucleophile in the reaction with alkylated 1,4-naphthoquinones **16** and **20**. However, regioselectivity is better controlled in the two step transformation via Stille reaction of bromoquinones (e.g. **24**) with allyl stannanes (e.g. **11**) followed by Lemieux-Johnson cleavage of the double bond. In contrast to anions generated from **8**, the Stille reaction is furthermore compatible with the presence of carbonyl groups in the second "bottom" side chain (see **3** Scheme 1).

Experimental

For general methods and instrumentation see [18].

Reaction of 2-methyl-1,4-naphthoquinone (16) with methyl 3-methoxybut-2-enecarboxylate (7)

A solution of methyl 3-methoxybut-2-enecarboxylate (**7**) [8] (1.82 g, 14 mmol) in dry THF (3 ml) was treated under argon at −20 °C with a solution of LDA (14 mmol) in dry THF (21 ml). After 0.5 h of stirring, a solution of 2-methyl-1,4 naphthoquinone (**16**) (1.00 g, 5.8 mmol) and dichloro-dicyano benzoquinone (DDQ) (1.45 g, 6.4 mmol) in dry THF (30 ml) was added at 0 °C. The mixture was allowed to warm to 0 °C and stirring was continued for 8 h. The mixture was quenched with diluted HCl (0.1 M, 150 ml) and extracted three times with diethyl ether (300 ml). The combined organic phases were washed with brine (200 ml), dried (Na_2SO_4), filtered, and the solvent was removed at reduced pressure. The residue was separated by column chromatography (CC) on silica gel (CH_2Cl_2/2% CH_3OH) to afford naphthoquinone **12** (680 mg, 39%, colorless solid, *m.p.* 98 °C.), **13** (420 mg, 24%, *m.p.* 164 °C, yellow needles), and **14** (120.0 mg, 8%, *m.p.* 128.5 °C, yellow needles).

Methyl 3-methoxy-4-(2-methyl-1,4-dioxo-1,2,3,4-tetrahydronaphthalene-2yl)-but-2-enecarboxylate (**12**)

IR (KBr): ν_{max} = 1696 cm^{-1} (ester CO), 1626 (CO), 1595 (arom. C=C). – UV (methanol): $\lambda_{max}(\varepsilon)$: 224 nm (4.51), 297

(3.29), 327 (2.78), 336 (2.77). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 1.35 (s, 3 H, C-2' CH_3), AB-system: [δ_A = 2.87 (d), δ_B = 3.16 (d), ($^2J_{AB}$ = 16.1 Hz, 2 H, 3'-H, 4-H)], AB-system: [δ_A = 3.23 (d), δ_B = 3.37 (d), ($^2J_{AB}$ = 13.3 Hz, 2 H, 3'-H, 4-H)], 3.35 (s, 3 H, ester-OCH_3), 3.65 (s, 3 H, ether-OCH_3), 5.02 (s, 1 H, 2-H), 7.70–7.75 (m, 2 H, 6'-H, 7'-H), 7.98–8.08 (m, 2 H, 5'-H, 8'-H). – ^{13}C NMR ($CDCl_3$, 50 MHz): δ/ppm = 24.99 (q, C-2' CH_3), 39.95 (t, C-3', C-4), 48.52 (s, C-2'), 50.15 (t, C-3', C-4), 51.33 (q, ester-OCH_3), 55.36 (q, ether-OCH_3), 94.18 (d, C-2), 126.30 (d, C-5', C-8'), 127.85 (d, C-5', C-8'), 134.03 (d, C-6', C-7'), 134.65 (d, C-6', C-7'), 134.89 (s, C-4a', C-8a'), 135.14 (s, C-4a', C-8a'), 167.95 (s, C-3), 171.48 (s, C-1), 196.08 (s, C-1', C-4'), 200.05 (s, C-1', C-4'). – MS (EI/60 °C): *m/z*(%) = 303 (8) [M^+ + 1], 302 (30) [M^+], 271 (44) [M^+ + 1 – CH_3OH], 270 (86) [M^+ – CH_3OH], 256 (10) [M^+ + 1 – (CH_3OH, CH_3)], 255 (54) [M^+ –(CH_3OH, CH_3)], 227 (50), 225 (70), 211 (42), 173 (38), 155 (30), 128 (100), 115 (24) [$C_5H_7O_3^+$], 84 (52).

$C_{17}H_{18}O_5$	Calcd. C 67.54	H 6.00
(302.33)	Found C 67.20	H 5.85

Methyl 3-methoxy-4-(3-methyl-1,4-dioxo-1,4-dihydronaphthalene-2yl)-but-2-enecarboxylate (**13**)

IR (KBr): ν_{max} = 3065 cm^{-1} (C–H), 2998, 2973, 2955. 2938, 1680 (ester CO),1611 (quinone CO), 1593 (arom. C=C), 1566, 1449. – UV (methanol): λ_{max}(lg ε) = 223 nm (4.44), 282 (4.19), 349 (4.10). – ^{1}H NMR ($CDCl_3$, 300 MHz): δ/ppm = 2.17 (s, 3 H, C-3' CH_3), 3.35 (s, 3 H, ester-OCH_3), 3.74 (s, 3 H, ether-OCH_3), 4.39 (s, 2 H, 4-H), 5.16 (s, 1 H, 2-H), 7.69–7.72 (m, 2 H, 6'-H, 7'-H), 8.08–8.11 (m, 2 H, 5'-H, 8'-H). – ^{13}C NMR ($CDCl_3$, 50 MHz): δ/ppm = 12.68 (q, C-3' CH_3), 28.79 (t, C-4), 50.82 (q, ester-OCH_3), 55.75 (q, ether-OCH_3), 91.06 (d, C-2), 126.08 (d, C-5', C-8'), 126.32 (d, C-5', C-8'), 131.80 (s, C-4a', C-8a'), 131.97 (s, C-4a', C-8a'), 133.17 (d, C-6', C-7'), 133.25 (d, C-6', C-7'), 142.40 (s, C-2'), 145.08 (s, C-3'), 167.76 (s, C-3), 171.45 (s, C-1), 183.87 (s, C-1', C-4'), 184.89 (s, C-1', C-4'). – MS (EI/50 °C): *m/z*(%) = 271 (4) [M^+ + 1 – (2 CH_3)], 270 (20) [M^+ –(2 CH_3)], 256 (18) [M^+ + 1 – (3 CH_3)], 255 (100) [M^+ –(3 CH_3)], 241 (4), 115 (3) [$C_5H_7O_3^+$].

$C_{17}H_{16}O_5$	Calcd. C 67.99	H 5.37
(300.31)	Found C 68.15	H 5.49

4-Hydroxy-2-methoxy-9a-methyl-1,9a-dihydroanthraquinone (**14**)

IR (KBr): ν_{max} = 3425 cm^{-1} (OH), 3065 (C–H), 2998 (C–H), 2955 (C–H), 1680 (CO), 1611 (CO), 1593 (arom. C=C), 1566. – UV (methanol): λ_{max}(lg ε) = 223 nm (4.27), 283 (4.05), 352 (3.97), 374 (3.93). – ^{1}H NMR ($CDCl_3$, 300 MHz): δ/ppm = 1.36 (s, 3 H, C-9a CH_3), AB-system: [δ_A= 2.71 (d), δ_B= 2.80 (d), ($^2J_{AB}$ = 17.7 Hz, 2 H, 1-H)], 3.82 (s, 3 H, OCH_3), 5.52 (s, 1 H, 3-H), 7.61 (dd, ^3J = 7.6 Hz, 1 H, 6-H, 7-H), 7.76 (dd, ^3J = 7.6 Hz, 1 H, 6-H, 7-H), 8.05 (d, ^3J = 7.6 Hz, 1 H, 5-H, 8-H), 8.10 (d, ^3J = 7.6 Hz, 1 H, 5-H, 8-H), 15.59 (s, 1 H, chelat.-OH). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ/ppm= 27.50 (q, 9a-C CH_3), 36.14 (t, C-1), 45.30 (s, C-9a), 56.22 (q, OCH_3), 99.75 (d, C-3), 108.35 (s, C-4a), 125.02 (d, C-5, C-8), 127.19 (d, C-5, C-8), 130.72 (s, C-8a, C-10a), 131.61 (d, C-6, C-7), 133.75 (s, C-8a, C-10a), 134.54 (d, C-6, C-7), 162.91 (s, C-2), 175.34 (s, C-4), 190.48 (s, C-9, C-10), 200.39 (s, C-9, C-10). – MS (EI/60 °C): *m/z*(%) = 271 (4) [M^+ + 1], 270 (18) [M^+], 256 (20) [M^+ + 1 – CH_3], 255 (100) [M^+ – CH_3], 241(4) [M^+ + 1 –(2 CH_3)], 223 (4) [M^+ + 1 – (2 CH_3, H_2O)], 183 (8), 165 (5), 139 (9), 105 (7).

$C_{16}H_{14}O_4$	Calcd. C 71.10	H 5.22
(270.28)	Found C 71.02	H 5.34

Dimethyl 4-Methyl-2,5-dioxo-3,5-dihydro-2H-cyclopenta[a]naphthalene-1,3-dicarboxylate (**15**)

A solution of dimethyl 3-oxopentanedicarboxylate (**5**) (2.0 g, 11.5 mmol) in dry THF (5 ml) was added under an atmosphere of argon to a suspension of NaH (290 mg, 12.1 mmol) in dry THF (20 ml). After ca. 10 min (no more H_2 is formed), the mixture was slowly added at –20 °C under argon to a solution of 2-methyl-1,4-naphthoquinone (**16**) (1.0 g, 5.8 mmol) in dry THF (20 ml). The greenish solution was allowed to warm to 20 °C and stirring was continued for 24 h. The reaction was stopped by addition of water (100 ml) and HCl (13 ml, 1 N) and the solution was extracted with diethyl ether (3× 100 ml). The organic phase was washed with brine, dried (Na_2SO_4), filtered, and the solvent removed at reduced pressure. The residue was purified by CC on silica gel (CH_2Cl_2/2% CH_3OH) to afford **15** (yellow plates, 94 mg, 6%; *m.p.* 113.5 °C).

$C_{18}H_{14}O_6$	Calcd. C 66.26	H 4.32
(326.31)	Found C 66.17	H 4.34.

IR (KBr): ν_{max} = 3081 cm^{-1}, 2961, 1748 (ester CO), 1705 (CO), 1647 (CO), 1595 (arom. C=C valenz. – UV (methanol): λ_{max}(lg ε) = 206 nm (4.38), 256 (4.18), 318 (4.44). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 2.12 (s, 3 H, C-4 CH_3), 3.80 (s, 3 H, OCH_3), 4.04 (s, 3 H, OCH_3), 4.41 (s, 1 H, 3-H), 7.62–7.75 (m, 2 H, 7-H, 8-H), 7.82–7.89 (m, 1 H, 6-H, 9-H), 8.25–8.31 (m, 1 H, 6-H, 9-H). – ^{13}C NMR ($CDCl_3$, 50 MHz): δ/ppm = 13.63 (q, C-4 CH_3), 53.74 (q, OCH_3), 53.80 (q, OCH_3), 54.93 (d, C-3), 128.16 (d, C-6, C-9), 128.51 (d, C-6, C-9), 128.86 (s, C-1, C-4, C-5a, C-9a), 131.94 (s, C-1, C-4, C-5a, C-9a), 133.32 (d, C-7, C-8), 133.42 (d, C-7, C-8), 134.14 (s, C-1, C-4, C-5a, C-9a), 135.07 (s, C-1, C-4, C-5a, C-9a), 143.61 (s, C-3a, C-9b), 153.61 (s, C-3a, C-9b), 164.92 (s, CO_2CH_3), 166.12 (s, CO_2CH_3), 183.48 (s, C-5), 192.25 (s, C-2). – MS (EI/100 °C): *m/z*(%) = 327 (2) [M^+ + 1], 326 (16) [M^+], 296 (6) [M^+ + 1-OCH_3], 295 (28) [M^+ – OCH_3], 294 (100) [M^+– 1– OCH_3], 267 (6) [M^+ – CO_2CH_3], 266 (10) [M^+ – 1 – CO_2OCH_3], 236 (26) [M^+ – (CO_2CH_3, OCH_3)], 235 (99) [M^+ – 1 –(CO_2CH_3, OCH_3)], 208 (8), 138 (10).

Methyl 3-Hydroxy-2-(3-methyl-1,4-dioxo-1,4-dihydronaphthalene-2-yl)-2-butenecarboxylate (**17**)

A solution of 6-methoxy-2,2-dimethyl-4-methylene-4*H*-[1,3,2]dioxasilin (**9**) [5] (3.00 g, 17.4 mmol) in THF (5 ml) was added slowly under argon at –60 °C to a solution of 2-methyl-1,4-naphthoquinone (**16**) (1.00 g, 5.8 mmol), 18-crown-6 (200 mg, 0.8 mmol) and CsF (900 mg, 5.9 mmol) in THF (50 ml). Stirring was continued at this temperature for 6 h, the mixture was allowed to warm to 22 °C, Ag_2O (1.4 g, 6.0 mmol) was then added, and the suspension was stirred for 1 h. The suspension was filtered, the solvent removed at reduced pressure, and the residue was purified by CC (CH_2Cl_2/2% CH_3OH) to afford quinone **17** as a yellow solid (180 mg, 11%); *m. p.* 138.5 °C. Alternatively, the product **17** (110 mg, 7%) was isolated in the reaction of the dianion of **6** [prepared

from **6** (1.35 g, 11.6 mmol) and LDA (2.2 equiv)] with quinone **16** (1.00 mg, 5.8 mmol).

$C_{16}H_{14}O_5$ Calcd. C 67.13 H 4.93
(286.28) Found C 67.27 H 5.08

IR (KBr): ν_{max}= 3432 cm^{-1} (OH), 2957 (C–H), 1663 (CO), 1647 (CO), 1595 (arom. C=C), 1447, 1291. – UV (methanol): λ_{max}(lg ε) = 215 nm (3.93), 252 (4.39), 260 (4.32), 322 (3.43), 332 (3.49). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 1.86 (s, 3 H, 4-H), 2.11 (s, 3 H, C-3' CH_3), 3.68 (s, 3 H, OCH_3), 7.70–7.78 (m, 2 H, 6'-H, 7'-H), 8.06–8.18 (m, 2 H, 5'-H, 8'-H). – ^{13}C NMR ($CDCl_3$, 50 MHz): δ/ppm = 14.81 (q, C-3' CH_3), 20.06 (q, C-4), 52.36 (q, OCH_3), 96.62 (s, C-2), 126.77 (d, C-5', C-8'), 127.08 (d, C-5', C-8'), 132.61 (s, C-4a', C-8a'), 132.67 (s, C-4a', C-8a'), 133.96 (d, C-6', C-7'), 134.08 (d, C-6', C-7'), 141.41 (s, C-2'), 147.31 (s, C-3'), 171.77 (s, C-1, C-3), 174.78 (s, C-1, C-3), 183.98 (s, C-1', C-4'), 185.78 (s, C-1', C-4'). – MS (EI/60 °C): *m/z*(%) = 287 (4) [M^+ + 1], 286 (18) [M^+], 271 (6) [$M^+ - CH_3$], 255 (22) [$M^+ + 1 - CH_3OH$], 254 (100) [$M^+ - CH_3OH$],244 (15), 239 (22) [M^+–(CH_3, CH_3OH)], 226 (36), 212 (80) [$M^+ - (CH_3, CO_2CH_3)$], 184 (52), 156 (18) [$M^+ - (CH_3, CH_3COCHCO_2CH_3)$], 43 (52) [$CH_3O^+$].

Reaction of 2-methyl-1,4-naphthoquinone (16) with 6-Methyl-2,2-dimethyl-[1,3]dioxine-4-one (8)

As described above for the reaction of **16** with the anion of **7**, 6-methyl-2,2-dimethyl-[1,3]dioxine-4-one (**8**) was reacted with 2-methyl-[1,4]naphthoquinone (**16**) (2.00 g, 11.6 mmol) for 2 h. The crude product mixture was separated by CC on silica gel (CH_2Cl_2/2% CH_3OH) to afford naphthoquinone **18** (1.12 g, 31%, *m.p.* 112.5 °C, yellow needles) and **19** (1.57 g, 43%, *m.p.* 98.0 °C, colorless powder). Alternatively, products **18** and **19** were formed in low yields (< 5%) in the reaction of **16** with the silyl ether **10** similarly as described for **17**.

2-(2,2-Dimethyl-6-oxo-6H-[1,3]dioxine-4-ylmethyl)-3-methyl-[1,4]naphthoquinone (**18**)

$C_{18}H_{16}O_5$ Calcd. C 69.22 H 5.16
(312.32): Found C 69.24 H 5.15.

IR (KBr): ν_{max} = 3000 cm^{-1} (C–H), 1727 (lactone CO), 1655 (quinone CO), 1622, 1593 (arom. C=C. – UV (methanol): λ_{max}(lg ε) = 204 nm (4.17), 252 (4.42), 332 (3.44). – ^{1}H NMR ($CDCl_3$, 300 MHz): δ/ppm = 1.66 (s, 6 H, acetonide-CH_3), 2.24 (s, 3 H, C-3 CH_3), 3.65 (s, 2 H, C-2 CH_2), 5.24 (s, 1 H, 5'-H), 7.72–7.77 (m, 2 H, 6-H, 7-H), 8.06–8.13 (m, 2 H, 5-H, 8-H). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ/ppm = 13.39 (q, C-3 CH_3), 24.96 (q, acetonide-CH_3), 30.94 (t, C-2 CH_2), 94.23 (d, C-5'), 106.93 (s, C-2'), 126.58 (d, C-5, C-8), 126.61 (d, C-5, C-8), 131.67 (s, C-4a, C-8a), 132.02 (s, C-4a, C-8a), 133.87 (d, C-6, C-7), 133.91 (d, C-6, C-7), 139.50 (s, C-2), 146.55 (s, C-3), 160.76 (s, C-4'), 167.66 (s, C-6'), 183.47 (s, C-1,C-4), 184.47 (s, C-1, C-4). – MS (EI/80 °C): *m/z*(%) = 314 (<0.1) [M^+ + 2], 313 (0.4) [M^+ + 1], 312 (<0.1) [M^+], 284 (0.1), 255 (6) [$M^+ + 1 - CH_3COCH_3$], 254 (26) [$M^+ - CH_3COCH_3$], 227 (6) [$M^+ + 1 - (CH_3COCH_3, CO)$], 226 (18) [$M^+ - (CH_3COCH_3, CO)$], 213 (6) [$M^+ + 1 - (CH_3CO\,CH_3, CO, CH_2)$], 212 (6) [$M^+ - (CH_3COCH_3, CO, CH_2)$], 186 (100) [$M^+ + 1 - C_6H_7O_3$], 128 (19) [$C_6H_8O_3^+$], 69 (32), 59 (22) [$CH_3COCH_3^+$ + 1], 58 (3) [$CH_3COCH_3^+$].

2-(2,2-Dimethyl-6-oxo-6H-[1,3]dioxine-4-ylmethyl)-2-methyl-2,3-dihydro-[1,4]naphthoquinone (**19**)

$C_{18}H_{18}O_5$ Calcd. C 68.78 H 5.77
(314.33) Found C 68.74 H 5.90

IR (KBr): ν_{max} = 2975 cm^{-1}, 2961, 1730 (lactone CO), 1694 (CO), 1628, 1590 (arom. C=C), 1391, 1269. – UV (methanol): λ_{max}(lg ε) = 223 nm (4.56), 253 (4.33), 303 (3.44). – ^{1}H NMR ($CDCl_3$, 300 MHz): δ/ppm = 1.37 (s, 3 H, C-2 CH_3), 1.61 (s, 3 H, acetonide-CH_3), 1.65 (s, 3 H, acetonide-CH_3), AB-system: [δ_A = 2.56 (d), δ_B = 2.77 (d), ($^2J_{AB}$ = 14.3 Hz, 1 H, 3-H, C-2 CH_2)], AB-system: [δ_A = 2.96 (d), δ_B = 3.12 (d), ($^2J_{AB}$ = 16.2 Hz, 2 H, 3-H, C-2 CH_2)], 5.26 (s, 1 H, 5'-H), 7.74–7.82 (m, 2 H, 6-H, 7-H), 8.01–8.10 (m, 2 H, 5-H, 8-H). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ/ppm = 24.51 (q, acetonide-CH_3), 24.86 (q, C-2 CH_3), 25.33 (q, acetonide-CH_3), 41.94 (t, C-3, C-2 CH_2), 48.15 (s, C-2), 49.87 (t, C-3, C-2 CH_2), 96.54 (d, C-5'), 106.83 (s, C-2'), 126.31 (d, C-5, C-8), 127.71 (d, C-5, C-8), 133.52 (s, C-4a, C-8a), 134.40 (d, C-6, C-7), 134.60 (s, C-4a, C-8a), 134.78 (d, C-6, C-7), 160.45 (s, C-4'), 167.37 (s, C-6'), 194.87 (s, C-1, C-4), 198.60 (s, C-1, C-4). – MS (EI/80 °C): *m/z*(%) = 316 (<0.1) [M^+ + 2], 315 (0.4) [M^+ + 1], 314 (1.2) [M^+], 257 (22) [$M^+ + 1 - CH_3COCH_3$], 256 (100) [$M^+ - CH_3COCH_3$], 241 (23) [$M^+ - (CH_3, CH_3COCH_3)$], 228 (42) [$M^+ - (CH_3COCH_3, CO)$], 210 (36) [$M^+ - (CH_3COCH_3, CO, H_2O)$], 188 (8) [$M^+ + 1 - C_6H_7O_3$], 187 (38) [$M^+ - C_6H_7O_3$], 186 (98) [$M^+ - 1 - C_6H_7O_3$], 173 (86) [$M^+ + 1 - (C_6H_7O_3, CH_3)$], 158 (52) [$M^+ + 1 - (C_6H_7O_3, 2\,CH_3)$], 59 (8) [$CH_3COCH_3^+$ + 1], 43 (36) [CH_3CO^+].

Reaction of Isoplumbagin (20) with 2,2-dimethyl-6-methylene-4-trimethylsiloxy-[1,3]diox-4-ene (10)

A solution of isoplumbagin (**20**) (300 mg, 1.6 mmol) in THF (30 ml) was treated at –78 °C under argon with $SnCl_4$ (415 mg, 1.6 mmol). After stirring for 0.5 h 2,2-dimethyl-6-methylene-4-trimethylsiloxy-[1,3]diox-4-ene [5] (**10**) (1.0 g, 4.7 mmol) was added. The mixture was stirred for additional 5 h, then quenched by addition of HCl (6N, 4 ml), and allowed to warm to 20 °C within 1 h. The solution was extracted with diethyl ether (100 ml), the organic phase was washed with water and then with a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4), filtered, and the solvent was removed at reduced pressure. The residue was separated by CC on silica gel (CH_2Cl_2/2% CH_3OH) to afford **22** (40 mg, 7.6%, *m.p.* 107 °C, colorless solid) and **19** (15 mg, 2.3%, dec.).

2-(2,2-Dimethyl-6-oxo-6H-[1,3]dioxine-4-ylmethyl)-8-hydroxy-2-methyl-2,3-dihydro-[1,4]naphthoquinone (**22**)

$C_{18}H_{18}O_6$ Calcd. C 65.45 H 5.49
(330.34) Found C 65.34 H 5.46

IR (KBr): ν_{max} = 3427 cm^{-1} (OH), 3094 (C–H), 2975 (C–H), 1723 (CO), 1696 (CO), 1647 (CO), 1630 (C=C), 1399, 1287, 1013, 907, 816. – UV (methanol): λ_{max}(lg ε) = 202 nm (4.27), 232 nm (4.53), 353 (3.90). – ^{1}H NMR ($CDCl_3$, 300 MHz): δ/ppm = 1.40 (s, 3 H, C-2 CH_3), 1.60 (s, 3 H, acetonide-CH_3), 1.65 (s, 3 H, acetonide-CH_3), AB-system: [δ_A = 2.51 (d), δ_B = 2.87 (d), ($^2J_{AB}$ = 14.8 Hz, 1 H, 3-H, C-2 CH_2)], AB-system: [δ_A = 2.92 (d), δ_B = 3.11 (d), ($^2J_{AB}$ = 15.9 Hz, 2 H, 3-H, C-2 CH_2)], 5.30 (s, 1 H, 5'-H), 7.30 (dd, ^2J = 8.3 Hz, ^3J = 1.2 Hz, 1 H, 5-H), 7.56 (dd, ^2J = 7.6 Hz, ^3J = 1.2 Hz, 1 H,

6-H), 7.68 (dd, ^2J = 7.6 Hz, ^2J = 8.3 Hz, 1 H, 7-H), 12.05 (s, 1 H, chelat. OH). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ/ppm = 24.67 (q, C-2 CH_3, acetonide-CH_3), 25.03 (q, C-2 CH_3, acetonide-CH_3), 25.13 (q, C-2 CH_3, acetonide-CH_3), 41.74 (t, C-3, C-2 CH_2), 47.56 (s, C-2), 49.17 (t, C-3, C-2 CH_2), 96.67 (d, C-5'), 106.69 (s, C-2'), 117.59 (d, C-7), 124.20 (s, C-8a), 124.30 (d, C-5), 134.53 (s, C-4a), 137.06 (d, C-6), 160.23 (s, C-4'), 162.09 (s, C-8), 166.73 (s, C-6'), 194.20 (s, C-1, C-4), 205.30 (s, C-1, C-4). – MS (EI/75 °C): *m/z*(%) = 331 (1) [M^+ + 1], 330 (5) [M^+], 273 (21) [M^+ + 1 – CH_3COCH_3], 272 (100) [M^+ – CH_3COCH_3], 254 (20) [M^+ –(CH_3COCH_3, H_2O)], 226 (25), 202 (58), 189 (58), 174 (16), 43 (6) [CH_3CO^+].

6-(5-Hydroxy-3-methyl-4-oxo-1-trimethylsilyanyloxy-1,4-dihydronaphthalene-1-ylmethyl)-2,2-dimethyl-[1,3]dioxine-4-one (**23**)

IR (KBr): ν_{max} = 3440 cm^{-1} (OH), 2955 (C–H), 1728 (lactone CO), 1661 (CO), 1628 (C=C), 1607, 1460, 1381, 1051. – UV (methanol): λ_{max}(lg ε) = 202 nm (4.08), 223 (3.97), 249 (4.09), 358 (3.50). – ^{1}H NMR ($CDCl_3$, 300 MHz): δ/ppm = – 0.09 (s, 9 H, $Si(CH_3)_3$), 1.42 (s, 3 H, acetonide-CH_3), 1.47 (s, 3 H, acetonide-CH_3), 2.04 (s, 3 H, C-3´ CH_3), AB-system: [δ_A = 2.74 (d), δ_B = 2.88 (d), ($^2J_{AB}$ = 13.6 Hz, 2 H, C-1´ CH_2)], 5.04 (s, 1 H, 5-H), 6.76 (s, 1 H, 2'-H), 6.94 (d, ^3J = 8.3 Hz, 1 H, 6'-H, 8´-H), 7.14 (d, ^3J = 7.7 Hz, 1 H, 6'-H, 8'-H), 7.52 (dd, ^3J = 8.3 Hz, ^3J = 7.7 Hz, 1 H, 7'-H), 12.47 (s, 1 H, chelat. OH). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ/ppm = 1.69 (q, Si $(CH_3)_3$), 15.50 (q, C-3' CH_3), 24.70 (q, acetonide-CH_3), 25.04 (q, acetonide-CH_3), 50.34 (t, C-1' CH_2), 71.66 (s, C-1'), 96.38 (d, C-5), 106.30 (s, C-2), 114.20 (s, C-4a'), 117.30 (d, C-6', C-8'), 117.78 (d, C-6', C-8'), 134.37 (s, C-8a'), 135.68 (d, C-2'), 146.84 (s, C-3'), 147.66 (d, C-7'), 160.64 (s, C-6), 162.09 (s, C-5'), 165.85 (s, C-4), 190.05 (s, C-4').

Dimethyl 3-Hydroxy-2-(5-hydroxy-3-methyl-1,4-dioxo-1,4-dihydronaphthalene-2-yl)-pent-2-enedicarboxylate (**21**)

A solution of isoplumbagin (**20**) (500 mg, 2.7 mmol) and dimethyl 3-oxopentandicarboxylate (**5**) (1.0 g, 5.7 mmol) in dry THF (50 ml) was stirred for 24 h at 22 °C. The mixture was filtered, Ag_2O (750 mg, 3.2 mmol) was added, and the suspension was stirred for 1 h. The suspension was filtered again, the solvent was removed at reduced pressure, and the residue purified by CC on silica gel (CH_2Cl_2/2% CH_3OH). In addition to unreacted starting material **20** (420 mg, 84%) compound **21** (48 mg, 5%; *m.p.* 133 °C; yellow solid) was isolated.

$C_{18}H_{16}O_8$	Calcd. C 60.00	H 4.48
(360.32)	Found C 59.92	H 4.59

IR (KBr): ν_{max} = 3449 cm^{-1} (OH), 2959 (C–H), 1736 (ester CO), 1655 (quinone CO), 1638 (quinone CO), 1456, 1443, 1354, 1254. – UV (methanol): λ_{max}(lg ε) = 210 nm (4.46), 274 (4.45), 424 (4.02). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.13 (s, 3 H, C-3´ CH_3), AB-system: [δ_A = 3.07 (d), δ_B = 3.21 (d), ($^2J_{AB}$ = 15.5 Hz, 2 H, 4-H)], 3.66 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 7.24–7.29 (m, 1 H, 7'-H), 7.57–7.66 (m, 2 H, 6'-H, 8'-H), 12.10 (s, 1 H, 5'-OH), 13.04 (s, 1 H, 3-OH). – ^{13}C NMR ($CDCl_3$, 50 MHz): δ/ppm = 14.35 (q, C-3' CH_3), 39.75 (t, C-4), 52.79 (q, OCH_3), 52.90 (q, OCH_3), 98.48 (s, C-2), 115.61 (s, C-4a'), 119.81 (d, C-6'), 124.48 (d, C-8'), 132.44 (s, C-8a'), 136.81 (d, C-7'), 141.26 (s, C-2'), 148.41 (s, C-3'), 161.88 (s, C-5'), 168.03 (s, C-1, C-5), 169.36 (s, C-1, C-5), 171.46 (s, C-3), 183.09 (s, C-1'), 190.63 (s, C-4'). – MS (EI/80 °C): *m/z*(%) = 361 (12) [M^+ + 1], 360 (65) [M^+], 329 (34) [M^+ + 1 –CH_3OH], 328 (72) [M^+ – CH_3OH], 301 (15) [M^+ – CO_2CH_3], 300 (15) [M^+ –1 – CO_2CH_3], 269 (14) [M^+ –(CH_2 CO_2 CH_3, H_2O)], 268 (28) [M^+ – 1 –(CH_2CO_2 CH_3, H_2O)], 254 (100) [M^+ –(CH_3, CO_2CH_3, CH_3OH)], 242 (12) [M^+ – (CO_2CH_3, CO_2CH_3)], 241 (72) [M^+ – 1 –(CO_2CH_3, CO_2 CH_3)], 228 (92), 115 (31), 59 (51) [$CO_2CH_3^+$].

2-Methyl-3-(2-methylallyl)-[1,4]naphthoquinone (**25**)

A solution of 2-bromo-3-methyl-[1,4]naphthoquinone (**24**) (500 mg, 2.0 mmol) in 1,4-dioxane (20 ml) was treated with $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) and CuBr (114 mg, 0.6 mmol) and *n*-tributyl-(2-methallyl)-stannane (**11**) [9] (760 mg, 2.2 mmol). After 7 h of reflux under argon the solvent was removed under reduced pressure, and the residue was purified by filtration over silica gel (petroleum ether, 33 % ethyl acetate) to afford the product **25** (417 mg, 93%, yellow oil).

IR (KBr): ν_{max} = 2959 cm^{-1} (C–H), 2924 (C–H), 1663 (quinone CO), 1597 (arom. C=C), 1294. – UV (methanol): λ_{max}(lg ε) = 204 nm (4.07), 247 (4.03), 269 (3.98), 327 (3.21), 336 (3.20). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 1.82 (s, 3 H, C-2' CH_3), 2.17 (s, 3 H, C-2 CH_3), 3.37 (s, 2 H, 1'-H), 4.59 (s, 1 H, 3'-H), 4.80 (s, 1 H, 3'-H), 7.58–7.80 (m, 2 H, 6-H, 7-H), 7.92–8.18 (m, 2 H, 5-H, 8-H). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ/ppm = 13.21 (q, C-2 CH_3), 23.64 (q, C-2' CH_3), 34.57 (t, C-1'), 111.68 (t, C-3'), 126.57 (d, C-5, C-8), 126.79 (d, C-5, C-8), 132.44 (s, C-4a, C-8a), 132.54 (s, C-4a, C-8a), 133.70 (d, C-6, C-7), 133.76 (d, C-6, C-7), 141.74 (s, C-2'), 144.89 (s, C-2, C-3), 145.36 (s, C-2, C-3), 184.58 (s, C-1, C-4), 185.42 (s, C-1, C-4). – MS (EI): *m/z*(%) = 227 (18) [M^+ + 1], 226 (98) [M^+], 212 (18) [M^+ + 1 – CH_3], 211 (100) [M^+ – CH_3], 199 (26), 177 (20), 105 (16), 55 (5) [$(CH_2)_2$ CCH_3^+], 41 (14) [$CH_2CCH_3^+$].

2-Methyl-3-(2-oxopropyl)-[1,4]naphthoquinone (**26**)

A solution of 2-methyl-3-(2-methylallyl)-[1,4]naphthoquinone (**25**) (500 mg, 2.2 mmol) in a mixture of 1,4-dioxane (65 ml) and water (65 ml) was treated with a solution of osmium tetroxide (5.5 ml, 2 × 10^{-2} M in *tert*-butanol) and $NaIO_4$ (517 mg, 2.4 mmol) and stirred for 24 h. Additional 517 mg of $NaIO_4$ were added and stirring was continued for 2 h. The mixture was diluted with water (110 ml) and extracted three times with diethyl ether. The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed at reduced pressure. The residue was purified by filtration over a short column of silica gel (CH_2Cl_2/2% CH_3OH) to afford the methyl ketone **26** (425 mg, 86%, *m.p.* 122 °C, yellow crystals).

$C_{14}H_{12}O_3$	Calcd. C 73.67	H 5.30
(228.24)	Found C 73.74	H 5.27

IR (KBr): ν_{max} = 2961 cm^{-1} (C–H), 2928 (C–H), 1713 (aliph. CO), 1680 (quinone CO), 1626, 1593 (arom. C=C). – UV (methanol): λ_{max}(lg ε) = 245 nm (3.99), 251 (4.00), 263 (3.88). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 2.14 (s, 3 H, C-2 CH_3), 2.33 (s, 3 H, 3'-H), 3.82 (s, 2 H, 1'-H), 7.68–7.73 (m, 2 H, 6-H, 7-H), 7.98–8.12 (m, 2 H, 5-H, 8-H). – ^{13}C NMR

($CDCl_3$, 50 MHz): δ/ppm = 13.28 (q, C-2 CH_3), 30.25 (q, C-3'), 41.72 (t, C-1'), 126.40 (d, C-5, C-8), 126.45 (d, C-5, C-8), 131.78 (s, C-4a, C-8a), 132.19 (s, C-4a, C-8a), 133.54 (d, C-6, C-7), 133.65 (d, C-6, C-7), 140.52 (s, C-2), 145.87 (s, C-3), 184.11 (s, C-1, C-4), 184.70 (s, C-1, C-4), 203.37 (s, C-2'). – MS (EI): *m/z*(%) = 228 (9) [M^+], 213 (98) [$M^+ - CH_3$], 186 (12) [$M^+ + 1 - CH_3CO$], 157 (14) [$M^+ + 1 - (CH_3, CH_2COCH_3)$], 128 (9), 115 (4), 104 (4), 77 (4), 59 (5) [$CH_3COCH_3^+ + 1$].

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